DESIGN AND SYNTHESIS OF BENZOPYRONE COMPOUNDS WITH POTENTIAL MEDICINAL APPLICATIONS

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ABSTRACT

The benzopyrones are a significant class of compounds that have potential uses in the medical field. They display a diverse array of biological activities, some of which include anti-inflammatory, antioxidant, anticoagulant, antiviral, and anticancer properties. In the course of this research, we devised and synthesized a wide range of new benzopyrone compounds in order to investigate the possible medical uses of these substances. The Michael addition reactions, the Claisen-Schmidt condensation, and the Knoevenagel condensation were among the several methods that were used in the synthesis of the benzopyrone derivatives. Many different types of spectroscopy, such as 1H-NMR, 13C-NMR, and IR spectroscopy, were used in order to investigate the structural make-up of the newly synthesized compounds. In vitro and in vivo examinations of the synthetic benzopyrone compounds' biological activity yielded exciting findings on the latter's possible use in the treatment of a variety of diseases. The findings of this research provide useful information that may be used to the formulation and synthesis of new benzopyrone molecules that could have uses in medicine.

Keywords:- *Benzopyrone, anti-inflammatory, antioxidant, anticoagulant, antiviral, and anticancer properties*

INTRODUCTION

The development of new medications is the primary emphasis of the scientific field of pharmaceutical chemistry, an interdisciplinary field that brings together elements of chemistry and pharmacy. It includes the conceptualization, discovery, synthesis, and development of novel chemical entities that are appropriate for use in therapeutic applications. Analyses of presently available medications, including those regarding their biological characteristics and quantitative structure-activity connections, are also presented.

A pharmaceutical drug is any chemical substance or product that is designed for use in the medical diagnosis, cure, treatment, or prevention of sickness. Pharmaceutical drugs include both generic and brand-name medications. In certain circles, it is also known as a medication or a medicine. The field of pharmaceutical chemistry is concerned with the quality of pharmaceuticals and tries to ensure that chemicals may be transformed into physiologically active forms that are appropriate for use in humans.

AN INTRODUCTION TO DRUG DEVELOPMENT AND DESIGN:

In the past, the term "drug discovery" exclusively referred to the processes of designing, synthesizing, analyzing, and testing novel chemical entities. These procedures were performed by synthetic chemists and were the only ones included in the definition. The majority of drug development up to the year 1980 was carried out in a sequential fashion[5]. The process of drug development and discovery is one that requires a significant investment of both time and resources due to the number of steps required, including

molecular design, synthesis, testing, and assessment.

These affects range from localized molecular and cellular interactions to systemic effects on the organism and process. Molecular and cellular interactions are on the smaller end of the spectrum.[6] A number of subfields within the area of drug research devote a significant amount of emphasis on meeting the regulatory standards imposed by drug licensing organizations. In the usual course of events, a number of research projects designed to identify the primary dangers posed by a new chemical are carried out before it is first tested on human subjects.

1. Natural Occurrence

The 4H-1-benzopyran-4-one ring system is a notable member of the family of oxygen heterocycles and may be found in a broad variety of plant species. In light of the fact that this naturally occurring benzopyran-4-one has some of the most advantageous curative qualities, several synthesized alternatives have been the subject of investigation. Compounds containing benzo-pyrone (chromone) or benzo-pyrone (coumarin) moieties are known to display a wide variety of biological effects.

2. 2H-1-benzopyran-2-ones Analogs

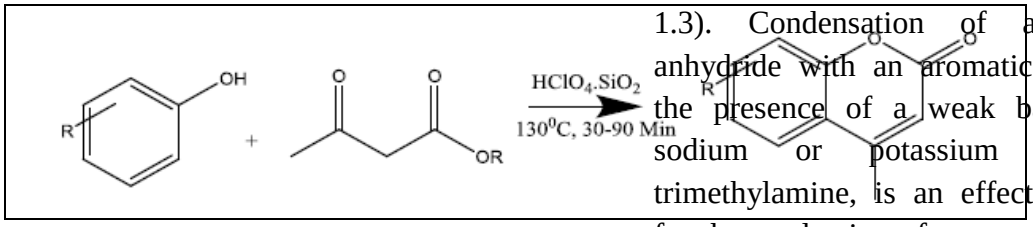
It has been discovered that substituted compounds of 2H-1-benzopyran-2-ones exhibit a wide variety of biological effects. Antibiotics as potent as Novobiocin, Coumaromycin, and Chartesium are found among the derivatives of 2H-1-benzopyran-2-ones. The use of these compounds as luminous markers in the biochemical analysis of enzymes is responsible for the recent resurgence in interest in these chemical substances.

BENZOPYRONE SYNTHETIC TRACES

Because of the prevalence of benzopyrone derivatives, a large number of researchers have developed exhaustive methods for the synthesis of molecules that either include the benzo-pyrone or the benzopyrone ring, leading to the synthesis of naturally occurring substances. These methods led to the development of naturally occurring substances. Either the necessary 2H-1-benzopyran-2-one with the appropriate substituent was added, or the necessary lactonic ring was closed with the required substituent in the benzene nucleus, in order to generate the naturally occurring 2H-1-benzopyran-2-one I. This might have been accomplished in one of two ways. A great deal of research has been put into the synthesis of 2H-1-benzopyran-2-one over the course of many years. This substance may be made in a number of ways, including those that are described here.

1. Von Pechmann reaction

The Pechmann condensation is one of the most common methods for producing 2H-1-benzopyran-2-one and the derivatives of this compound. This method requires the reaction of phenol with a -ketoester, such as ethyl acetoacetate or methyl acetoacetate, in the absence of a solvent and in the presence of an acidic catalyst. In this procedure, heterogeneous catalysts like $HClO_4.SiO_2$[49] are often utilized as reactants (Scheme-1.1). A few of the many benefits of the process include short reaction times, minimal catalyst costs (which may be recovered), and an average high yield of products ranging from 65 to 97%. These benefits are only a few of many.

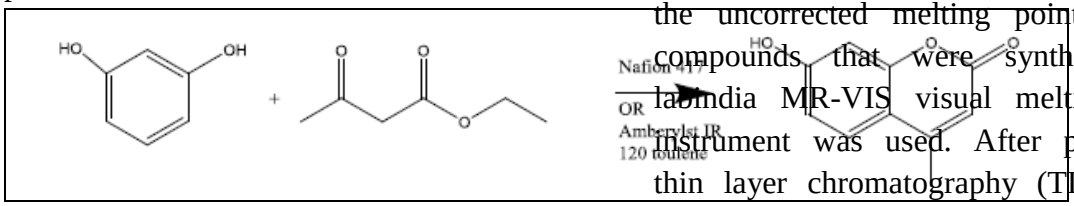


Where R=Et or Me

Scheme-1.1: Von Pechmann reaction

The reaction may also be catalyzed by a variety of Brnsted and Lewis acids, such as PPA[50], $InCl_3$[51], $ZrCl_4$[52], $Yb(OTf)_3$[53], p-TsOH[54], $BiCl_3$[55], and I2 or AgOTf[56]. Several of these acids are listed in the above sentence. Recent efforts in green chemistry have resulted in attempts to replace stoichiometric solid Brnsted and Lewis acids with non-stoichiometric substances such as montmorillonite clay[57] and cation exchange resin[58]. The use of ionic liquid was also noted in reference number [59].

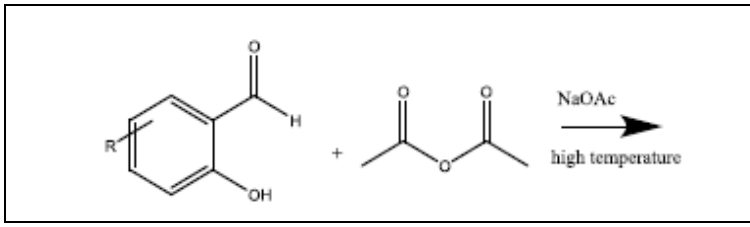
Toluene was used as the solvent, and acidic catalysts such as Amberlyst IR120 or Nafion 417 were used for the Pechmann condensation synthesis of substituted 2H-1-benzopyran-2-one that was reported by Thimons et al.[60]. This synthesis began with substituted phenols and ethyl acetoacetate. (Scheme-1.2). A limitation of this technique is the poor item yield it produces.



Scheme-1.2 :Modified Von Pechmann reaction

2. Perkin reaction

1868 was the year when Perkin published his findings that the reaction of sodium salt of salicylaldehyde with water solution at a high temperature and a molar ratio of 1:2 created 2H-1-benzopyran-2-one (Scheme-1.3). Condensation of a carboxylic anhydride with an aromatic aldehyde in the presence of a weak base, such as sodium or potassium acetate or trimethylamine, is an effective approach for the production of unsaturated aromatic acids (Scheme-1.3). In spite of the fact that the 2H-1- benzopyran-2-one, also known as coumarin, is produced in low yield and is then followed by the synthesis of tarry materials, the Perkin procedure has the benefit of not producing the isomeric chromene[61].



Scheme-1.3: Perkin reaction

SYNTHESIS AND CHARACTERIZATION

1. Materials and method

The firms gave the researchers access to their chemical and reagent supplies (Merck, SD fine, Rankem labs, Sigma Aldrich and HiMedia). Using thin-layer chromatography, the reactions are being seen and analyzed. In order to determine the uncorrected melting points of the compounds that were synthesized, a labindia MR-VIS visual melting range instrument was used. After performing thin layer chromatography (TLC) using silica gel1 to determine the purity of the newly produced compounds, the compounds were then recrystallized with the help of the suitable solvents.

COMPUTATIONAL ANALYSIS BENZOPYRONES AS ANTI-DIABETIC AGENTS

Hyperglycemia is the end consequence of the metabolic condition known as diabetes mellitus, which is characterized by improper insulin production or usage. According to a research published by the WHO, diabetes mellitus would be among the top 10 causes of death in the year 2030. The existing state of things suggests that it will be difficult to produce hypoglycemic treatments that are effective at treating diabetes and at preventing diabetic complications.

This is the case because developing hypoglycemic drugs requires a lot of research and testing. Intestinal enzymes such pancreatic amylase and alpha glucosidase are responsible for the conversion of ingested carbohydrates into the simpler sugars maltose and glucose, which leads to an increase in blood glucose levels after a meal. These enzymes will be prevented from functioning properly, which will stop the breakdown of carbohydrates.

BENZOPYRONES AS ANTI-OXIDANT AGENTS

It's possible that the definition of oxidative stress has been altered as a result of an imbalance between the production of free radicals and the body's capacity to employ inhibitor mechanisms to minimize the consequences of those radicals. Free radicals are characterized by the presence of unpaired electrons in unstable atoms, molecules, or ions. Some examples of free radicals are reactive atomic number species (ROS), reactive nitrogen species (RNS), and reactive sulfur species (RSS). According to research24, free radicals have been linked to a wide variety of chronic diseases and ailments, such as Parkinson's disease, Alzheimer's disease, cancer, and inflammatory illnesses. So, the development of brand new synthetic compounds is very necessary in the area of contemporary medication design and research if we are going to prevent such catastrophic medical conditions.

METHODOLOGY:

Docking is a method that may be used on a computer to try to find potential ligand binding activities that take place in the active region of a receptor. A grid of interaction points denotes the region of an image that is currently being used. After that, the ligand is positioned appropriately in the binding site by the use of either a grid search or an energy search. The grid search, which is also known as an energy search, is carried out by calculating the binding energy (G bin) between the receptor and the ligand using the following equation. This process is also known as doing an energy search.

The expression "G bind" may be written as "G receptor plus G ligand minus G receptor plus G ligand complex."

When determining the amount of energy required to bind, a number of different interactions between receptors and ligands are included in. These interactions include vanderwaal's interaction, electrostatic interactions, and aromatic interactions.

In order to handle the diversity sampling issue in a way that is more practically applicable, computational methods33 have been developed. This strategy may be streamlined via the use of molecular modeling, which also restricts the quantity of compounds to a specified number. This is necessary since it is impossible to manufacture and assess each and every possible chemical.

1. The methodology can be divided into following steps:

• Importing protein files, ligand files, and ligand preparation.
• Making protein and locating protein molecule cavities.
• Using the docking wizard panel to carry out a docking setup.
• Establishing the positions of the protein-ligand complex
• Hydrogen Bond Interaction and Mol Dock Score Calculation

2. Importing a protein file, ligand file and preparation of ligands

Using the construct and optimization method, the two-dimensional structure of the ligand molecules (benzopyrones) was transformed into a three-dimensional structure, which was afterwards cleaned up in three dimensions. Upon completion of the structure, it was then stored in the MDL Molfile format (*.mol). Each properly submitted input structure resulted in the creation of a singular, three-dimensional structure that was low in energy and included the requisite chiralities.

When the structures were developed, they were imported into the workspace of the docking program known as Molegro virtual Docker 6.0. MDL, which stands for "sdf/sd/mol/mdl," is a file format that provides bonding data. This format may be used to add the molecule to MVD. At this point in the process, the creation of the test compound included assigning many properties, including charges, bonds, bond order, charges, explicit hydrogens, flexible torsion in ligands, and hybridization. Table 4.1 contains an inventory of the various ligands' three-dimensional structures.

3. Protein preparation and detecting cavities of protein molecules

After the construction of the electrostatic surface of the receptor site, a grid-based cavity prediction method was used in order to locate the places most likely to be occupied by binding molecules. It's possible that the receptor's binding site may make room for the ligand. When determining the amount of energy required to bind, a number of different interactions between receptors and ligands are included in.

These interactions include Vanderwaal's interaction, electrostatic interactions, and aromatic interactions. The two protein receptors (PDBs) that were employed in this research were designated as 1US0 aldose reductase and 3SE2 PARP1 inhibitor.

BIOLOGICAL EVALUATION

The phrase that is used to describe the impact that a medicine has on living creatures is known as the drug's biological activity or its pharmacological activity. 1 If a drug is a complex chemical combination, any active component or pharmacophore will display this activity; however, other factors may modify it. This holds true even if the activity is altered. It is normal for the effects of a single medicine to shift from being useful to being harmful when moving from low amounts to large quantities since activity is often dose-dependent.

The ADME rules need to be followed throughout activity. The primary goal of research conducted in the biological sciences is to locate a therapeutic agent that is suitable for usage in humans. 2. The term "pharmacological activity" is often used to characterize positive results, such as those of drug candidates3, despite the fact that a chemical is termed "bioactive" if it interacts with the cell tissues of the human body.

The following two primary kinds of studies are carried out in order to determine the biological activity of the chemicals that have been synthesized:

1. In vitro studies (Antimicrobial activity)

The study of microorganisms, which are often too tiny to be seen without the use of a microscope, is the primary focus of the field of microbiology, which is a subfield of biology.

2. In vivo studies (Pharmacological activity)

Pharmacological study (In vivo) on animals plays an important role in the identification of new molecules with selective pharmacological activities which may be used clinically.

CONCLUSION

Medical chemistry focuses on the invention, characterisation, and interpretation of the chemical processes that lie behind physiologically active substances. These are the primary goals of the field. The primary structural component of a great deal of flavonoid compounds is referred to as benzopyrone, which is a word for ketone derivatives of benzopyran. In an attempt to find novel compounds that are more effective for use in pharmacological settings, we investigated the biological effects of benzopyrone derivatives and the manufacturing processes involved in their creation.

The material included in this thesis is broken down and presented to the reader in the form of five chapters.

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